Remarks

Claims 46-50, 55, 57-86 are pending in the subject application. Entry and consideration of the arguments presented herein is respectfully requested. Accordingly, claims 46-50, 55, 57-86 are currently before the Examiner and favorable consideration of the pending claims is respectfully requested.

Submitted herewith is a supplemental Information Disclosure Statement (IDS), accompanied by the form PTO/SB/08, and a copy of the reference listed therein. Applicants request that the reference in the IDS be made of record in the subject application.

Applicants gratefully acknowledge the Examiner's withdrawal of the rejections under 35 U.S.C. §§ 102 and 112, first paragraph.

Claims 46-50, 55 and 57-86 are rejected under 35 U.S.C. § 112, first paragraph, as nonenabled by the subject specification. The Office Action has made of record the Taimr *et al.* reference and indicates that they teach that extensive liver fibrosis, which results from the deposition and accumulation of type I collagen within the liver parenchyma, results in fibrosis. The Office Action also indicates that Taimr *et al.* state that understanding the mechanisms of liver fibrosis is essential to defining anti-fibrotic therapies. Taimr *et al.* is cited as teaching that activated hepatic stellate cells have been established as the source of type I and III collagen in the liver. Applicants respectfully assert that the claims as filed are enabled. The Office Action indicates that the specification fails to teach how to treat a fibrotic disease *in vivo* using fragments and/or mutants of full length INSP035 (SEQ ID NO:2). The Office Action claims that the specification provides no guidance as to which regions of the INSP035 protein would be tolerate of modification and which would not, and it provides no working examples of any variant sequence. The Office Action states that the specification fails to teach the structural features that are required in order to provide the biological activity of inhibiting fibrosis. Accordingly, reconsideration and withdrawal of the rejection under 35 U.S.C. § 112, first paragraph, is respectfully requested.

The Office Action dated June 15, 2011 argues that the as-filed specification fails to enable one to make and/or use the claimed invention. In this respect the Office Action argues that the as-filed specification teaches that INSP035 is able to counteract the apoptotic effect of soluble human recombinant TRAIL on fibroblasts, thereby consistently reducing the apoptosis of the fibroblasts;

however, Taimr *et al.* is cited for a purported teaching of an opposite biological effect. Namely, that if TRAIL can induce selective apoptosis of activated stellate cells, it would become a candidate anti-fibrotic agent. The Office Action further argues that Taimr *et al.* teach that TRAIL agonists are useful as anti-fibrotic agents whereas the specification teaches that INSP035 (a TRAIL antagonist) is useful for the treatment of fibrosis. Applicants respectfully disagree with the arguments set forth in the Office Action.

First, Taimr *et al.* teach, based on *in vitro* data, that at a high, non-physiological concentrations *(i.e.* 1 μg/ml), exogenous TRAIL strongly induces apoptosis of activated stellate cells (see Figures 5 and 7). Thus, the authors conclude that a TRAIL agonist may be a good candidate for treating fibrosis by inducing apoptosis of activated hepatic stellate cells.

These results were subsequently confirmed by Yurovski *et al.* (cited in the attached Information Disclosure Statement). Indeed, Yurovski *et al.* reported that exogenous TRAIL strongly induces apoptotic death in lung fibroblasts at concentrations of 100 ng/ml or higher (see page 229, right column, 1st paragraph and Figure 2). However, Yurovski *et al.* also teach that at concentrations of 10 ng/ml or lower (*i.e.*, more physiological levels of TRAIL), exogenous TRAIL stimulates fibroblasts into extracellular matrix (ECM) production, notably collagen type I production (see Figure 7). This activity on ECM production appears involving the TGFβ pathway (see Figure 6). Applicants also note that Yurovski *et al.* also teach that physiological concentrations of TRAIL are estimated at about 1 ng/ml, (page 229, Discussion, paragraph 2). Finally, Yurovski *et al.* also teach that "Taken together, these data indicate that TRAIL, at doses below the apoptosis-inducing threshold, can upregulate ECM production by fibroblasts. The mechanisms of this stimulation likely involve triggering the TGF-β pathway of autocrine and paracrine activation of fibroblasts. If this process continues uncontrolled, it may contribute to the development of fibrosis, particularly in the lungs of patients with systemic sclerosis. The molecular crosstalk observed between TRAIL and TGF-β signaling pathways may be the target for therapeutic intervention" (see page 230, paragraph bridging columns 1-2). This reference, thus, suggests the TRAIL/TGFβ signaling pathway as a target for treating fibrosis in typical physiological settings.

In the present application, it is shown that INSP035 polypeptide is capable of inhibiting exogenous TRAIL activity *in vitro:* Example 2 demonstrates that INSP035 is an inhibitor of TRAIL-

mediated apoptosis at TRAIL concentrations of about 2 ng/ml (see also Figure 1). From Yurovski *et al.*, it is known that at such a concentration, exogenous TRAIL induces collagen production in fibroblasts. Thus, based on the results presented in the pending application and on the fact that TRAIL stimulates collagen production at low concentrations, the results presented in the pending application teach one skilled in the art that INSP035 could be used to reduce collagen deposition mediated by TRAIL pathway and treat fibrotic disease. Thus, Applicants respectfully submit that there is no contradiction between the teaching of Taimr *et al.* and the pending application. Indeed, Taimr *et al.* show, similar to the teachings of Yurovski *et al.*, that exogenous TRAIL at nonphysiological concentration induces apoptosis of activated stellate cells. The pending application shows that under physiological conditions, INSP035 is capable of counteracting TRAIL activities, related to collagen production. Accordingly, reconsideration and withdrawal of this aspect of the rejection is respectfully requested.

The Office Action also argues that "the specification fails to teach how to treat a fibrotic disease in vivo using fragments and/or mutants of full length INSP035" and that "the disclosure provides no guidance as to which regions of the INPS035 protein would be tolerant of modifications". It is further argued that because SEQ ID NOs: 5 and 7 contain one-half the number of amino acid residues as SEQ ID NO: 2, "it is in no way predictable that randomly selected mutations, deletions, etc. in the disclosed sequence would afford a protein having activity comparable to the one disclosed". The Office Action concludes that "undue burden would be required of the skilled artisan to make and/or use the claimed invention in its full scope". Applicants respectfully disagree and traverse the rejection of record.

At the outset, Applicants note that the pending claims do not recite fragments and/or mutants of INSP035 full length (corresponding to SEQ ID NO:2) nor polypeptides having random mutations or deletions. Rather, the claims recite polypeptides comprising or consisting of SEQ ID NOs. 5 or 7, *i.e.* polypeptides comprising or consisting of definite sequences, shown to display similar activity as SEQ ID NO:2 on TRAIL inhibition *in vitro* (see page 7, lines 18-22 and page 27, line 7). It is further noted that Example 5 of the present invention describes an assay for testing the activity of INSP035 in bleomycin treated mice (a mouse model of lung fibrosis). Applicants also note that polyhistidine labeled forms of SEQ ID NOs: 2, 5 and 7 have been demonstrated to inhibit TRAIL activity (see

Figure 1 and the discussion of Figure 1 at page 7, lines 18-22). In that passage, it is stated that "INSP035-His Modified Medium Long Form (SEQ ID NO: 8) in TRAIL assay. Y-axis represents the percentage of TRAIL inhibition. X-axis represents the log dilution of the modified medium form of INSP035. **Similar curves were obtained with SEQ ID NO: 3 (INSP035-His Long Form) and SEQ ID NO: 6 (INSP035-His Medium Form)**" (emphasis added). The as-filed specification teaches that SEQ ID NOs: 3, 6 and 8 are polyhistidine labeled forms of SEQ ID NOs: 2, 5 and 7 (see the as-filed specification at page 8, lines 24-26). Thus, the as-filed specification provides evidence that the claimed polypeptides are capable of inhibiting TRAIL activity.

The Office Action also compared the *in vitro* effects of INSP035 with those of leptin (stated to belong to the same family) and concluded that "it is no way predictable that mutations, deletions, etc. in the disclosed sequence would afford a protein having activity comparable to the one disclosed". Applicants respectfully submit that this argumentation is not applicable to the pending application and, as noted above, the present application demonstrates that SEQ ID NOs:5 and 7 have comparable activity to SEQ ID NO:2. Therefore, the skilled person reading the pending application would know that the mature form of INSP035 (SEQ ID NO:2), a specific fragment thereof (SEQ ID NO:5) as well as a specific mutant thereof (SEQ ID NO:7) have similar activities and, contrary to the statement made in the Office Action, one skilled in the art would not be required to engage in undue experimentation in order to practice the claimed invention.

Finally, Applicants note that the pending application provides sufficient written description that enables a person skilled in the art to practice the claimed invention. For example, the as-filed specification provides teaching as to how one is to administer the claimed polypeptides for the treatment of lung or liver fibrosis and the as-filed specification also provides teaching as to how one is to make the claimed polypeptides (SEQ ID NOs: 2, 5 and 7). Accordingly, Applicants respectfully submit that the claimed invention is enabled by the as-filed specification and reconsideration and withdrawal of the rejection of record is respectfully requested.

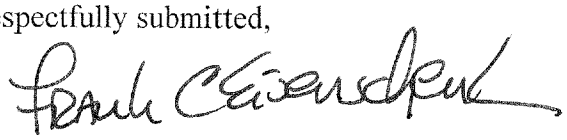
Applicants expressly reserve the right to pursue the invention(s) disclosed in the subject application, including any subject matter canceled or not pursued during prosecution of the subject application, in a related application.

In view of the foregoing remarks, Applicants believe that the currently pending claims are in condition for allowance, and such action is respectfully requested.

The Commissioner is hereby authorized to charge any fees under 37 CFR §§1.16 or 1.17 as required by this paper to Deposit Account No. 19-0065.

Applicants invite the Examiner to call the undersigned if clarification is needed on any of this response, or if the Examiner believes a telephonic interview would expedite the prosecution of the subject application to completion.

Respectfully submitted,



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